REMARKS

Status of the Claims

Claims 1, 4, 5, 9, 11-18 and 20-25 are currently pending in the application. Claim 1 has been amended as set forth herein without prejudice or disclaimer. No new matter has been added by way of the present amendments. For instance, the above amendment to claim 1 is supported by the content of the application as filed, for example by previous claims 1 and 10. Claim 10 has been cancelled without prejudice or disclaimer. Claims 14, 16 and 18 have been amended to remove dependency from cancelled claim 10. The amendments that are or have been made are made without acquiescing to the Examiner's rejection and shall in no circumstance be considered as an abandonment of the relevant subject-matter.

In view of the following remarks, reconsideration is respectfully requested.

Rejections under 35 U.S.C. § 103(a)

Claims 1, 4, 5, 9-12 and 20-25 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Kalionis in view of Vona.

Claims 13, 14, 16 and 17 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Kalionis in view of Vona and further in view of Bianchi.

Claim 15 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Kalionis in view of Vona and Fodor.

Claim 18 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Kalionis in view of Vona, and further in view of Pinkel.

Applicants traverse these rejections as set forth in their Replies of November 28, 2006 and of March 28, 2007, the entireties of which are incorporated herein by reference as if each and very statement were represented herein, to address each and every rejection listed above.

More specifically, Applicants maintain that neither Kalionis nor Vona, nor any of other references cited by the Examiner, disclose a step corresponding to step b) of claim 1.

The method of Kalionis comprises:

- filtering a sample of the maternal blood,
- **collecting the cells that are retained on the filter, and then**
- submitting the collected cells to **immunostaining** with trophoblast-reactive antibodies, to identify the trophoblast cells, **and then**
- submitting the immunostained cells to ***in situ*** **hybridization**.

Hence, both the nature and the order of the method steps of Kalionis differ from the steps of the presently claimed invention, as recited in claim 1. In the Kalionis reference, there is no step corresponding to isolation of a cell of fetal origin.

Furthermore, the method of Kalionis is suitable for late stage gestation (7½ months of gestation), but not for early stage, contrary to the claimed invention (5 weeks of gestation), which implies that the method of Kalionis is not enabled for pre-natal diagnosis. Thus, the cited prior art is not enabling for the presently claimed invention. A reference that lacks an enabling disclosure may qualify as a prior art reference under 35 U.S.C. § 103, but only for what is disclosed in it: "[i]n order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method." (*See*, *Beckman*

Instruments Inc. v. LKB Produkter AB, 13 U.S.P.Q.2d 1301, 1304 (Fed. Cir. 1989), citing *In re Payne*, 606 F.2d 303, 314, 203 U.S.P.Q. 245, 255 (CCPA 1979)).

Applicants maintain that, starting from the Kalionis reference, a person of average or ordinary skill in the art has to change everything in the disclosed method to arrive at the method of the claimed invention, and that the Kalionis reference does not address the problem of pre-natal diagnosis. Further, neither this reference, nor any other cited, provides the motivation to make these changes in the prior art method. Applicants respectfully submit that it is not *prima facie* obvious to modify a reference unless the references suggest an advantage to be gained from the modification. (*See*, *In re Sernaker*, 217 U.S.P.Q. 1, 6 (Fed. Cir. 1983)).

The Vona reference relates to the ISET method.

In the Vona reference, there is only one single assay comprising both ISET and RT-PCR.

This (ISET + RT-PCR) assay is performed on an epithelial tumor cell line, namely the Hep3B cell line. In this assay, all the cells that are retained on the ISET filter are tumor cells, whereas, in the presently claimed method, the cells that are retained on the filter are a complex population comprising different cell types in mixture, namely fetal and maternal cells. In the Vona reference, there is no cell isolation step at all.

In contrast, the method of the presently claimed invention explicitly addresses this problem. One of ordinary skill in the art understands that this problem is particularly difficult to address due to the difficulty in isolating the cell. Trophoblast cells in such samples of maternal blood are quite rare. Thus, there is a huge technical gap between the situation faced in the Vona reference and the one faced and solved by the present Inventor.

In fact, **the Vona reference fails to disclose a step corresponding to step b) of the presently claimed method,** i.e., a step which would comprise cytologically analyzing the cells before collecting an appropriate cell therefrom, i.e., a cell, the (fetal) origin of which would be presumed.

The Vona reference suggests testing whether ISET would be applicable to the filtration of trophoblast cells. However, this reference does not suggest applying (ISET + RT-PCR) or (ISET + PCR), or more precisely (ISET + **cytological analysis + PCR), to trophoblast cells.**

Furthermore, **the Vona reference fails to disclose a method, wherein the amplification step would comprise the demonstration of two clinical features.**

It is submitted that neither the disclosure of Kalionis nor the disclosure of Vona, as well as none of the other disclosures of the cited references, including the Bianchi, Fodor and Pinkel references, teach or suggest all the claim limitations when considered in combination.

Furthermore, in addition to those comments presented in the Replies of November 28, 2006 and March 28, 2007, although Applicants do not agree that the claims are obvious in light of the cited references, to expedite prosecution, Applicants have amended claim 1 as presented herein without prejudice or disclaimer, to specify that, prior to step f), the pre-amplification product of step e) is purified to obtain a preparation of preamplified DNA derived from the genome of said single cell.

Therefore, none of the disclosures of the cited references, more specifically none of the disclosures of Kalionis, Vona, Bianchi, Fodor and Pinkel, either considered individually or in combination, disclose or suggest this additional purification step.

It is further submitted that the presently claimed invention relates to a very specific problem, i.e., the problem of pre-natal diagnosis, and that it involves trophoblast cells, i.e., cells that are very rare in the maternal blood. The presently claimed invention cannot be equated to any standard kind of cell analysis, such as the standard assays discussed in the cited references.

The amendments of the claims presented herein are believed to adequately address all of the Examiner's comments presented in the Office Action of May 16, 2007.

That is, it is believed that the references, either considered individually or in combination, do not disclose or suggest all of the limitations recited in the presently amended claims. In light of the above comments and amendments, reconsideration and withdrawal of the obviousness rejection of claims 1, 4, 5, 9, 11-18 and 20-25 are respectfully requested. Issuance of a Notice of Allowability is thus requested.

CONCLUSION

If the Examiner has any questions or comments that may assist in prosecution of the present application, please contact Thomas J. Siepmann, Ph.D, Registration No. 57,374, at the offices of Birch, Kolasch & Birch, LLP.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

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Respectfully submitted,

By _____ #42,874

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